

in claim 2; and  $R_a$  is a suitable leaving group.

#### REMARKS

Applicant has carefully reviewed and considered the Office Action mailed on October 10, 2001, and the references cited therewith. Applicant respectfully request reconsideration of the rejection of claims in view of the foregoing amendments and the following remarks.

Claims 1, 2, 21-22, 26-27, 31, 33, 35, 39, 41, 49, 50 and 52 are amended; as a result, claims 1-52 are now pending in this application.

Support for the claim 2 amendment for the " $R^{46}$  and  $R^{47}$  together" clause is contained in the specification as filed, for example, on page 7, lines 24-28, and page 19, lines 15-28. The redrawn structures of A140 and A142 on page 42, and A577 on page 73, were made to correct typographic errors. Claims 1, 2, 21-22, 26-27, 31, 33, 35, 39, 41, 49, 50 and 52, and the specification have been amended as indicated to correct various obvious and inadvertent typographical errors. No new matter has been added by these amendments.

#### §112 Rejection of the Claims

Claims 21 [?, claim 22], 41 and 42 were rejected under 35 USC § 112, first paragraph, as based on a disclosure which is allegedly not enabling. The rejection is respectfully traversed.

Specifically, the Examiner has indicated that Claims 21, 41 and 42 each refer to areas of the specification as claimed subject matter. In other words, the Examiner has indicated that these claims define the claimed subject matter by reference to sections of the specification.

In paragraph 2 of the official action the Examiner indicated that claim 21 was not enabled. Applicant's representative has reviewed claim 21 and find it fully enabled and believe that the Examiner instead may have intended to reject claim 22. Consequently, Applicants have amended claim 22 as indicated to remove the reference to "shown hereinabove" and to add a proper reference to Table 1 ( contained in the specification on pages 31 to 75), which table illustrates the enumerated and claimed  $L_2$  radicals of claim 22.

A claim may refer to a table in the specification where the verbiage necessary to define the subject matter described therein would be so extensive (here 44 pages) and involved as to

defeat the very purpose of the claim. See *In re Faust* (Dec. of Superv. Exam. 1943) 86 USPQ 114; *Ex parte Maya et al.*, 156 USPQ 428. Similarly, radicals defined by reference to their values set forth in the specification does not render a claim improper under 35 USC § 112, second paragraph. See *Ex parte Moon*, 224 USPQ 519. Thus *In re Mayhew* cited by the Examiner is believed to be inapplicable to the claims as amended. In light of the amendments to the claims and the above remarks, withdrawal of the rejection of claim 22 is respectfully requested. It is noted that the amendment to claim 22 did not narrow the claim. Accordingly, a full scope of equivalents is available for the claim.

Regarding claims 41 and 42, it is respectfully pointed out that these claims depend from claim 2, and that the structure of the "group of formula (d)" is shown in claim 2. Accordingly, claims 41 and 42 do not "refer to areas of the specification as claimed subject matter," as suggested by the Examiner. Accordingly, withdrawal of the rejection of claims 41 and 42 is respectfully requested.

Claim 1 was rejected under 35 USC § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The rejection is respectfully traversed.

The Formula (I) and (a) were alleged not to "recite how  $L_2$ , in formula (a), attaches to the X substituent of formula (I)." As a first point, it is noted that formula (a) is a recited value for  $L_1$ , not for  $L_2$  as suggested by the Examiner. Additionally, it is respectfully submitted that it is clear from formula (I) ( $L_1$ -X- $L_2$ ) that  $L_2$  is bonded to the group X. The Examiner's attention is also directed to the specification as filed which contains numerous exemplary and preferred linkages or bonding relationships of  $L_1$  and  $L_2$  to the linker X. See for example, Schemes A-C and the accompanying discussion on pages 83-97. Thus, there is no ambiguity regarding the relationship of X and  $L_2$ .

Regarding the relationship between X and  $L_1$ , it is submitted that the definitions of B,  $R^2$ , Het,  $R^3$ , and  $R^5$  to  $R^8$  specifically state that these groups are possible sites of attachment for  $L_1$  to X. This information, in conjunction with the proviso "provided that at least one of the  $R^3$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ , "Het", heterocycloamino, or heteroaryl amino groups attaches (a) to a linker" found near the bottom of claim 1, makes it clear how  $L_1$  is attached to linker X. Therefore, there is also no

ambiguity regarding how L<sub>1</sub> is attached to linker X. In light of these remarks, it is submitted that it would be clear to one skilled in the art how L<sub>1</sub>, X, and L<sub>2</sub> are attached. Accordingly, claim 1 meets the requirements of 35 USC § 112, second paragraph, and withdrawal of the rejection is requested.

Claims 1 to 52 were rejected under 35 USC § 112, first paragraph, because the specification allegedly, while being enabling for specifically defined compounds when the substituents are specific, does not reasonably provide enablement for compounds where, for example the substituents are heterocyclic, heterocycloxy, thioheterocycloxy heteroaryl, heteroarylthio, heteroaryloxy, and heteroaralkyl. This rejection is respectfully traversed.

The Examiner has the initial burden to provide evidence to support a rejection under 35 U.S.C. § 112, first paragraph. The Examiner has failed to provide any evidence or reasoning to support the conclusion that the instant specification fails to provide adequate guidance to enable one skilled in the art to practice the claimed invention. Thus the Examiner has not met the burden required to establish a rejection under 35 U.S.C. § 112. Accordingly, withdrawal of the rejection is respectfully requested.

Additionally, the first paragraph of 35 U.S.C. § 112 requires no more than a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. Factual considerations outlined by the court in *In re Wands* include: (1) the quantity of experimentation necessary (time and expense); (2) the amount of direction or guidance presented; (3) the presence or absence of working examples relating to the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. The determination that undue experimentation would have been needed to practice the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all factual considerations, including the eight factors identified above. *In re Wands*, 8 U.S.P.Q.2d at 1404 (Fed. Cir. 1988). The Examiner failed to provide any analysis using these factors.

The specification provides 17 pages of general synthetic schemes illustrating how compounds of formula (I) can be prepared (pages 82-97); provides detailed information

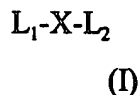
regarding utility, testing and administration (pages 98-101); describes the preparation of 146 specific compounds of formula (I); provides biological data for representative compounds of the invention in four separate assays (pages 113-117) and provides specific details regarding numerous assays that can be carried out by one skilled in the art to assess the biological activity of a compound of formula (I) (pages 113-119). Additionally, it is pointed out that medicinal chemistry is a well established field, where one skilled in the art typically possesses a graduate degree and often some post-graduate experience.

In light of the maturity of the relevant field and the extensive direction provided in the specification, it is respectfully submitted that one skilled in the art could practice the claimed invention without the need for undue experimentation. Thus, Applicant's specification meets the enablement requirement of 35 U.S.C. § 112, first paragraph. It is respectfully submitted that the rejection should be withdrawn.

§103 Rejection of the Claims

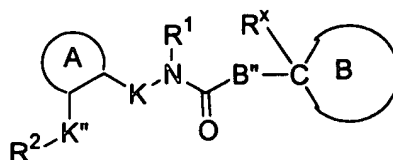
Claims 1 to 52 were rejected under 35 USC § 103(a) as being unpatentable over Takeuchi et al. (EP 0747355). The rejection is respectfully traversed.

The present claims (1-49) recite a compound having the following formula (I):



wherein:

$L_1$  is a group of formula (a):



(a).

Claims 50-51 recite a compound of formula  $L_1-H$ , and claim 52 recites a compound of the formula  $R_a-X-L_2$ .

The Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. M.P.E.P. §2142. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves, or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the teachings of the references. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. M.P.E.P. §2142. It is respectfully submitted that the Examiner has failed to establish any of these three criteria.

The instant claims (1-51) recite compounds with an R<sup>x</sup> group attached at the junction of the B ring and the B'' atom wherein R<sup>x</sup> is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, acyl, acylamino, aminoacyloxy, aryl, carboxyalkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, heteroaralkyl, alkylsulfonyl, or alkylsulfinyl. The compounds discussed by Takeuchi lack this R<sup>x</sup> group. Thus, the compounds recited by claims 1-51 are outside the broad group of compounds discussed by Takeuchi. It is respectfully submitted that Takeuchi provides no motivation to modify the compounds discussed therein in the manner necessary to provide a compound recited by claims 1-51. Furthermore, Takeuchi provides no suggestion that the compounds discussed therein would retain any useful property if they were structurally modified in the manner necessary to provide a compound recited by the instant claims. Finally, Takeuchi does not suggest all of the elements of the compounds recited in claims 1-51, since the compounds discussed in Takeuchi lack the group R<sup>x</sup>.

Claim 52 recites intermediate compounds of the formula R<sub>a</sub>-X-L<sub>2</sub>. X and L<sub>2</sub> are defined in claim 2 where X is a linker and L<sub>2</sub> can be any of the formulas (b) to (e). R<sub>a</sub> is a suitable leaving group such as halo (e.g. chloro, bromo, or iodo), methylsulfonyl, 4-tolylsulfonyl, mesyl, or trifluoromethylsulfonyl and as defined in the specification at page 95, lines 6-18. Compounds of the formulas R<sub>a</sub>-X-L<sub>2</sub> and -X-L<sub>2</sub> of the present invention are outside the group of compounds discussed by Takeuchi, since Takeuchi does not teach compounds of the formula -X-L<sub>2</sub>. Takeuchi provides no motivation to modify the compounds discussed therein in the manner necessary to provide a compound recited by claim 52. Additionally, Takeuchi does not suggest

all of the elements of the compounds recited in claims, such as compounds including the formula -X-L<sub>2</sub> of the present invention. Therefore, the criteria required to establish a *prima facie* case of obviousness have not been met. Accordingly, withdrawal of the rejection under 35 U.S.C. §103 is respectfully requested.

Finally, the Examiner's attention is directed to page 10, lines 9-14, where it is reported that compounds of the present invention "have longer metabolic half-lives and/or longer duration of action *in vivo*, which can reduce the dose required for administration or can reduce the likelihood of the generation of unwanted metabolites." Thus, the compounds recited by the instant claims possess unexpected and advantageous properties. These improved properties are not suggested by Takeuchi.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612-359-3265) to facilitate prosecution of this application.


If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on this 7th day of February, 2001.

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